ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

AT THE

MASSACHUSETTS EYE AND EAR INFIRMARY

1970

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Here is the Annual Report of the Howe Laboratory for 1970. I hope you will glance through it, if for no other reason than to appreciate the conscientious performance by a group of investigators dedicated to ophthalmic research. The year has had its quota of satisfactions and disappointments, as is the nature of pioneering efforts, but we feel there has been a net gain which is decidedly on the plus side and, we hope, warrants the generous support which has been given us by our many friends.

David G. Cogan

David G. Cogan, M. D.

The Howe Laboratory is now approximately 40 years old, more or less — more if one dates it from the time of its official acceptance by the Harvard Medical School and its allocation to rooms in the Physiology Department and the Bussey Institute, or less if one dates it from its physical removal to the Massachusetts Eye and Ear Infirmary. Much has changed in these 40 years. The politics of the world and of medicine, the methods of financing, the occurrence of several wars and the changing emphases in scientific and social goals, all have necessitated continual accommodation to variable external and internal needs. But the aims have changed little. The unfaltering goal of the Howe Laboratory has been to bring basic sciences to bear on ophthalmic problems, to facilitate contact of the "bench scientist" with the clinical practitioner, and, thereby, to challenge the forces of disease and blindness.

Studies on cataracts, glaucoma, neuro-ophthalmology, ocular physiology, ophthalmic pathology, instrumentation and other fields which have been repeatedly documented in these Annual Reports are interesting (and to some of us absorbing) but the durable question which we continually ask ourselves is what are the humanitarian dividends in terms of health, education, and welfare. We are not always satisfied with our answers but we are comforted by small gains and exhilarated by the occasional "breakthroughs" which have punctuated the life history of the Laboratory.

In its 40 years the Laboratory has received generous support from many persons and agencies both within and outside the medical profession. Less than one quarter of its budget comes from endowment income. A substantial contribution is made each year by patients who, having personal knowledge of one disease or another, have contributed to research in their particular areas of interest. An increasing number of persons have elected to commemorate friends or relatives by contributions in this beneficent manner. A substantial contribution has been made by physicians who have included the Howe Laboratory in their annual philanthropies. Others have contributed to the Laboratory's several educational enterprises and some funds have been turned back into the Laboratory by members of its own staff. While these many sources add up to a considerable support, large grants have been made by the National Institutes of Health, the Massachusetts Lions Club, The Max, Martha and Alfred Stern Fund, the Scaife Family, The Permanent Charity Fund of Boston and Research to Prevent Blindness, Inc. We are most fortunate in having such rapport with benevolent persons and agencies who share with us the aim of learning all we can about the eye and its diseases. To them we dedicate this Annual Report.

GLAUCOMA

Research on glaucoma and intraocular fluid dynamics has come to occupy a large part of the Howe Laboratory's functions. Practically all the relevant activities revolve about Dr. Grant who doubles as Chief of the Infirmary's Glaucoma Consultation Service and central investigator in the Laboratory. The following is Dr. Grant's report for the past year.

Glaucoma, for the first-time reader of these reports, is still one of the most serious eye problems. About 2% of the population have glaucoma in some form, and it is one of the principal causes of permanent loss of vision. Fundamentally it is a simple condition consisting of pressure in the eye greater than it should be, and greater than the optic nerves can stand. Normally the eye is kept filled with clear fluid that is constantly secreted into the eye, and glaucoma is due simply to obstruction of the normal flow of this fluid out of the eye back to the bloodstream. However, there are more than three dozen different forms of glaucoma in which there are different kinds of obstruction, and in which the obstruction is produced by a variety of diseases. It occurs at all ages. Many treatments both by medicine and by surgery help in relieving and sometimes in curing glaucoma, but the type of treatment has to be appropriate to the type of glaucoma. In a great many patients there is serious need for better understanding of the causes of the obstruction and need for development of better and more specific means for relieving glaucoma. Fortunately glaucoma is receiving a great deal of attention, as reflected in the publication of 400 to 500 scientific articles concerned with the subject per year, and good progress is being made. This necessitates research at all levels from the laboratory to the clinic and operating room.

The way in which research on glaucoma is carried out illustrates a particular function of the Howe Laboratory, providing correlation of laboratory and clinical investigations. It has seemed to work best when physicians who have been confronted with the problems of the patient, and have been impressed with the need for further research, have come to the laboratory to explore the fundamentals of the problem with the aid and guidance of full-time members of the staff, both medical and non-medical scientists with a background of experience in both clinical and basic research.

Fortunately there are many who, particularly during their clinical residency training in ophthalmology, come to appreciate the pressing problems in glaucoma, and want to help resolve some of the problems through their own research. Those who have had full-time post residency glaucoma research fellowships and those who at a later stage in their careers, variously as friends, colleagues, consultants and supporters of the Howe Laboratory, have continued with their special interests and efforts in the study and treatment of glaucoma, are responsible for a great deal of the continuing progress in this field. In the past year, in the category of post residency research fellows we have been fortunate to have Dr. Bruce Ellingsen for a year, and for shorter terms, Dr. Joseph Michon, Dr. Brent Lambert and Dr. Paul Richards. As constant mentor, collaborator and supporter, Dr. Paul Chandler has provided a background of vast clinical experience and an inspirational stimulus in his nearly daily coffee conferences in the Howe Laboratory. Dr. David Walton has been dividing his time between clinical research on glaucoma, particularly in children, at the Howe Laboratory and clinical pediatric ophthalmology at the Children's Medical Center.

A good example of the correlation of Laboratory and clinical investigations that is favored and fostered by the Howe Laboratory is a program of research that has been carried out by Dr. Ellingsen, later assisted by Drs. Michon, Lambert, and members of the resident staff of the Infirmary. Dr. Ellingsen became intrigued with the properties of the aqueous outflow channels of the eye during his clinical residency. He recognized how important it would be to obtain a better understanding particularly of the functional physical characteristics of these channels so that we might understand better how they become obstructed in glaucoma and how we might better relieve the obstruction. Rather than depart for a lucrative practice, Dr. Ellingsen joined the Laboratory to make careful measurements on the resistance to fluid flow through the outflow channels of the eyes of people who had died and willed their eyes to ophthalmic research and also to make measurements on the eyes of monkeys, since comparison would prove valuable in further research. In human eyes Dr. Ellingsen found several important things. Taking care to avoid disturbance of the position of the lens and iris, he found that when the pressure in the human eye was raised, there was an increase in resistance to flow of fluid out of the eye, as though the pressure itself tended to collapse and occlude the outflow channels. Eyes from patients who had glaucoma showed this increase in obstruction to outflow even more markedly. By performing microdissections and making further measurements, Dr. Ellingsen obtained evidence that most of the resistance to outflow and also the influence of pressure on resistance to outflow could be eliminated. This was accomplished by trabeculotomy, removing trabecular meshwork and endothelial tissue, to give the intraocular fluid direct access to Schlemm's canal. Experimental evidence was obtained that when the intraocular pressure was raised, Schlemm's canal collapsed and it appeared probable that it was the compression of the trabecular and endothelial tissue that was responsible for raising resistance to outflow when intraocular pressure was elevated.

At this point Dr. Ellingsen's investigations turned to analysis of the action of an operation known as sinusotomy, which consisted of exteriorizing Schlemm's canal without intentional disturbance of the trabecular meshwork. This operation had been reported by Russian surgeons to be effective in reducing the pressure in glaucoma. They had supposed that this result indicated that the principal obstruction to outflow of fluid in many glaucomatous eyes was peripheral to Schlemm's canal, but this was contrary to the evidence that had been obtained here from trabeculotomy indicating that the principal resistance to outflow was on the internal side of Schlemm's canal. Further investigations in the laboratory by Dr. Ellingsen corroborated the Russian claim that sinusotomy was indeed effective in reducing resistance to aqueous outflow, but did not support the interpretation of "scleral" glaucoma assumed by the Russian investigators. Instead, Dr. Ellingsen's experiments indicated that when the sclera and outer wall of Schlemm's canal were removed, the trabecular meshwork and internal endothelial wall of Schlemm's canal had essentially nothing to press against, and as intraocular pressure was raised, instead of compressing trabecular meshwork and collapsing Schlemm's canal, it apparently caused outward bulging and stretching of the remaining tissues, causing them to allow intraocular fluid to pass through and escape more easily.

In the course of these laboratory studies Dr. Ellingsen not only contributed to the sound and logical basis for microsurgical procedures such as trabeculotomy and sinusotomy, but gained the knowledge and technical proficiency necessary for proceeding to the clinical phase of investigation.

The clinical phase was then undertaken by Dr. Ellingsen with the aid of Drs. Michon and Lambert. In this phase, special consideration was given to examining the circumstances under which operations of these types might be expected to offer advantages over older well-established procedures. The microsurgical procedures on Schlemm's canal were then applied in those cases in which they seemed to offer the greatest advantage to the patient. Also at this clinical phase of the investigation, another aspect of the outflow system for intraocular fluid was examined, this time in the eyes of normal human volunteers, including those of the investigators. This special aspect was a measurement of the pressures encountered beyond Schlemm's canal. Ordinarily the outflow of intraocular fluid from the eye to the bloodstream is opposed not only by the resistance in the outflow channels of trabecular meshwork, Schlemm's canal and sclera, but also is opposed by some 8 to 10 mm Hg venous back-pressure in the recipient blood vessels. However, when the outer wall of Schlemm's canal and the overlying sclera are excised, the intraocular fluid is no longer confined to vascular channels, but can escape into subconjunctival tissue spaces, To determine what influence this might have on the back-pressure opposing aqueous outflow, measurements were made by pumping salt solution (resembling intraocular fluid) into normal subconjunctival tissues at the normal rate of outflow. There it was found to encounter a back-pressure of only 1 or 2 mm Hg, which was significantly lower than the venous back-pressure of intact eyes. By-passing the vascular channels thus was another factor helping to explain the reduction of intraocular pressure obtained by sinusotomy, if this was not later affected by scarring and other changes in the tissues. This also would be a factor in explaining the reduction obtained by older standard filtering types of operations. Undoubtedly later postoperative scarring of the extraocular tissues can change this, but at least initially it offers a real advantage, and in some cases may continue to function in this manner.

In the course of the clinical phase of these investigations of microsurgery of Schlemm's canal, difficulties were learned of and modifications were made. Seeking improvement in particular for trabeculotomy, in which there is a problem of trying to prevent reclosure of a surgical opening, Dr. Ellingsen introduced diathermy trabeculolysis, accomplishing a destruction of the tissues between Schlemm's canal and the anterior chamber of the eye by introducing a fine wire electrically insulated on all but one side into Schlemm's canal, and then passing a momentary high frequency current. This makes a wider opening through the trabecular meshwork than most previous mechanical procedures.

While this transition from laboratory studies to clinical investigation and application was going on, it was obvious that to explore more radical and experimental medical and surgical procedures aimed at relieving obstruction to outflow of intraocular fluid in glaucoma, use of monkeys would offer greater freedom for innovation, if sufficient were known about how the eyes of monkeys compared with the eyes of human beings. Therefore, while the investigations on human eyes were proceeding as already described, investigations on eyes of monkeys were carried on, showing first that there was a definite similarity to the human eye with respect to the normal anatomical distribution of resistance to outflow of intraocular fluid, that in the monkey eye most of the resistance to outflow could be removed, as in the human eye, by removing the trabecular meshwork and endothelial layer between the anterior chamber and Schlemm's canal. However, measurements of resistance to outflow as intraocular pressure was raised, and lowered indicated that the outflow channels were not subject to compression and occlusion in quite the same manner as those of the human eye. When microsurgical procedures were performed on Schlemm's canal on living monkeys, a considerably greater reaction and tendency for openings in the tissues to close again was observed. These differences between the eyes of human beings and monkeys, plus the fact that monkeys are not subject to glaucoma in the way in which human beings are, suggest that research concerning glaucoma in monkeys may indeed be valuable as a pilot or preliminary stage, but that the applicability to human beings is uncertain. Studies on human eyes and clinical investigation are essential to obtaining definitive results applicable to patients.

Dr. David Walton, whose special field of interest is pediatric ophthalmology and who has already enlightened us with his studies and original observations on childhood glaucoma, has made a comprehensive survey of the extensive clinical data collected by Dr. Grant in cases of aniridia with glaucoma. Dr. Walton has also examined the pathology of this condition. In this case he has recognized what appears to be the probable mechanism underlying changes in the angle of the anterior chamber that are seen gonioscopically in aniridic children with glaucoma, and which was a mystery unresolved by extensive clinical studies. Dr. Walton has found that cells resembling the type that are normally found on the back surface of the cornea are present in aniridia in the angle of the anterior chamber and on the tiny stump of congenitally defective iris, in some cases forming a glassy membrane on these structures, analogous to formation of Descemet's membrane on the cornea. Associated with this misplaced layer of cells on the trabecular meshwork and iris stump are sheets of tissue belonging to the stump of defective iris itself, usually seen extending forward. Clinically the iris stump has been seen to move gradually forward to overlie outflow channels and obstruct the outflow of intraocular fluid. Drs. Walton and Grant postulate that it is this abnormal layer of cells that pull the iris stump forward.

In clinical studies on children with glaucoma associated with congenital aniridia, Drs. Grant and Walton have observed that the glaucoma has tended to become more severe during childhood, and in some cases this worsening of the glaucoma has been associated with a progressive distortion of the iris stump and progressive covering of openings of outflow channels by tissue from the stump. The experience of Dr. Grant and others in attempting to relieve this glaucoma by microsurgery of the angle, making fine incisions in the tissue overlying the outflow channels, seldom gave more than temporary relief, quite different from the results often obtained in other forms of congenital glaucoma in which this type of surgery, so-called goniotomy, often has given long lasting relief or cure. From the clinical observations both the progressive nature of the glaucoma in some cases and the poor responsiveness to goniosurgery seemed mysterious and inexplicable. Dr. Walton's study now has provided an explanation that makes the clinical characteristics of this special kind of glaucoma more understandable. It also shows why we must look for other ways of relieving this peculiar and difficult type of glaucoma.

Dr. Walton has extended his studies to other conditions in which cells resembling endothelium have been observed forming a membrane in areas of the anterior part of the eye where they did not belong. Possibly if we can learn more about the fundamental nature of this aberrant membrane formation we may be able to make a more logical approach to treating or preventing the glaucoma associated with congential aniridia.

Dr. Joseph Michon, who previously has reported fundamental studies on influence of anticholinesterase miotics on lens biochemistry, had glaucoma research projects in progress when he had to leave for military service. Dr. Michon sought information on one aspect of the mysterious condition "pseudoexfoliation", in which a gray powdery dandruff-like material appears in various locations in the anterior part of the eye and is often accompanied by glaucoma, possibly due to obstruction of fluid outflow channels by this material. Where this material comes from is still uncertain. It has been thought by some to come from the lens of the eye and by others from the ciliary body. Dr. Michon carefully examined patients who had had their lenses removed surgically because of cataracts, and who had been reliably known to have this pseudoexfoliation material in their eyes before operation. He wanted to know whether this material tended to disappear after the lens was removed from the eye, but his studies gave no indication of disappearance, and the patient examined at the longest interval after removal of the lens still had the pseudoexfoliation material after 7 years. This naturally is a factor of importance in the study and treatment of the associated glaucoma if it is in fact due to obstruction of outflow channels by this same material.

Dr. Michon with Dr. Alex Gaudio had in progress an evaluation of a procedure for treating glaucoma by low temperature transient freezing of the ciliary body, so-called cyclocryo treatment, finding a sufficient proportion of patients benefited, at least temporarily, to fully justify the further utilization and study of this form of treatment in certain types of glaucoma.

Dr. Michon started a study which is now being carried on by Dr.

Joseph Kim, examining the characteristics of Schlemm's canal observable in patients by making blood reflux from the veins into the canal where it is visible with a biomicroscope through a special suction gonioscopic contact lens. This technique for examining Schlemm's canal has been devised and described by other investigators, some of whom have concluded that a difference could be seen between normal and glaucomatous eyes. Since potentially this could be an important factor in the study and treatment of glaucoma, Dr. Michon and Dr. Kim have undertaken an independent evaluation. The first stage has consisted of a thorough study of the characteristics of Schlemm's canal as revealed by this technique in patients with normal eyes, preparatory to comparisons with the glaucomatous.

Dr. Brent Lambert participated with Dr. Ellingsen and Dr. Michon in microsurgical studies on Schlemm's canal and helped instruct a number of residents and also graduates of the residency in the special techniques. Dr. Lambert undertook an appraisal of methods for potentially and practically improving measurements of visual fields of glaucoma patients, and undertook a survey of peripheral retinal changes in patients having glaucomato-cyclitic crises, comparing the affected eyes with the contralateral normal eyes. Unfortunately Dr. Lambert had to leave for military service before these projects could be carried very far.

Dr. Robert Gorn, who had developed special expertise in ultrasonography, has several times provided significant helpful information in the study of patients who have had unusual forms of glaucoma, providing information from ultrasonographic measurements on whether the length of the eye has been abnormal, whether intraocular tumors might be present but hidden by cataracts, and on whether detachments of the retina and choroid might be present, similarly hidden from view by cataracts.

Dr. David Donaldson has continued through his development and application of stereo color photography of the optic nervehead to provide a precise record essential for a long term study of the ways in which glaucoma can gradually affect the optic nerve and cause associated losses of vision in certain peculiarly vulnerable portions of the visual fields. If this study can be carried on for a sufficiently long time, it should provide information that would be valuable not only for a study of mechanism of damage of the optic nerve by glaucoma, but also of direct practical clinical value in guidance of control and treatment of glaucoma and in estimation of prognosis in individual patients.

Dr. Stephen Fricker has been investigating the very reasonable possibility of analyzing the temporal characteristics of the ocular pulse as detected by electronic tonometry in relation to the beat of the heart detected by the electrocardiogram, with the expectation of demonstrating characteristic disturbances in the transmission of the pulse from the heart to the eye in cases in which there are obstructions or other abnormalities of the arteries conducting blood from the heart to the eye. This project is at an exploratory stage at present.

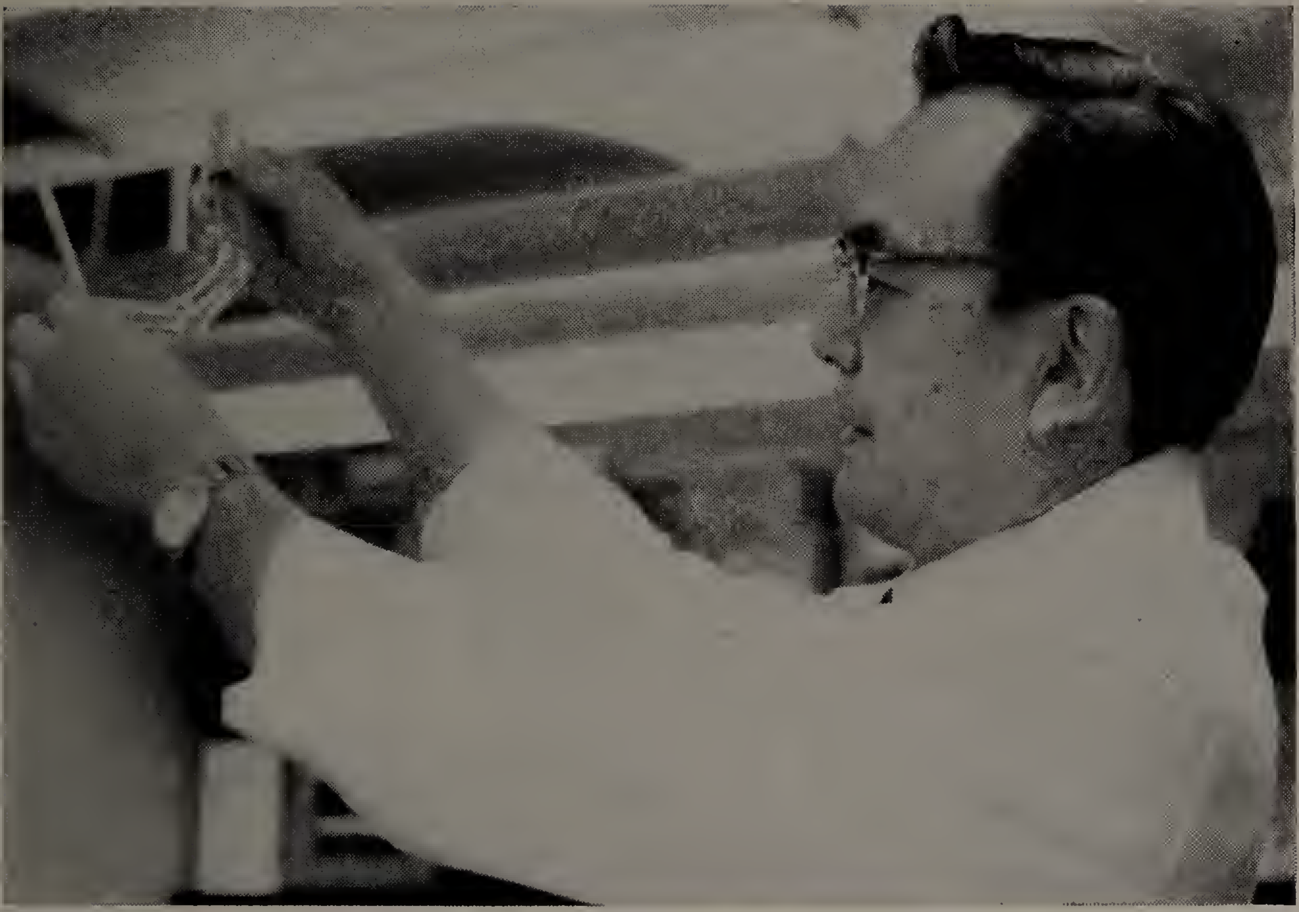
Dr. Grant, apart from providing what assistance and guidance he could to the various people mentioned in glaucoma research, has been evaluating whether tonographic measurements made on patients with their ciliary muscles paralyzed by cycloplegic eyedrops might distinguish glaucomatous from normal eyes better than tonography carried out in the standard manner, but so far it has appeared that cycloplegia tends to make the measurements on obviously glaucomatous eyes more abnormal, and has little influence on obviously normal eyes, but unfortunately seems to have little or no differential influence on eyes that are equivocal by ordinary testing.

Dr. Grant might have done more research on glaucoma himself if he had not been spending so much time preparing a second edition of Toxicology of the Eye, which includes much information on the influence of drugs on intraocular pressure.

BIOCHEMISTRY

Cataracts and Aldose Reductase

As noted in previous years, Dr. Kinoshita and his co-investigators have demonstrated the crucial role of aldose reductase in the formation of experimental cataracts. This enzyme triggers the mechanism leading to the development of cataracts encountered in diabetes and galactosemia. By use of inhibitors of this enzyme, it has been found possible to prevent the development of these sugar cataracts both in the test tube and, by intraocular injection, in the living animal. Current studies are directed to finding suitable inhibitors with appropriate permeability properties that will be effective when given by



Dr. Kinoshita examines one of the incubation tubes containing a lens that will be subjected to metabolic studies.

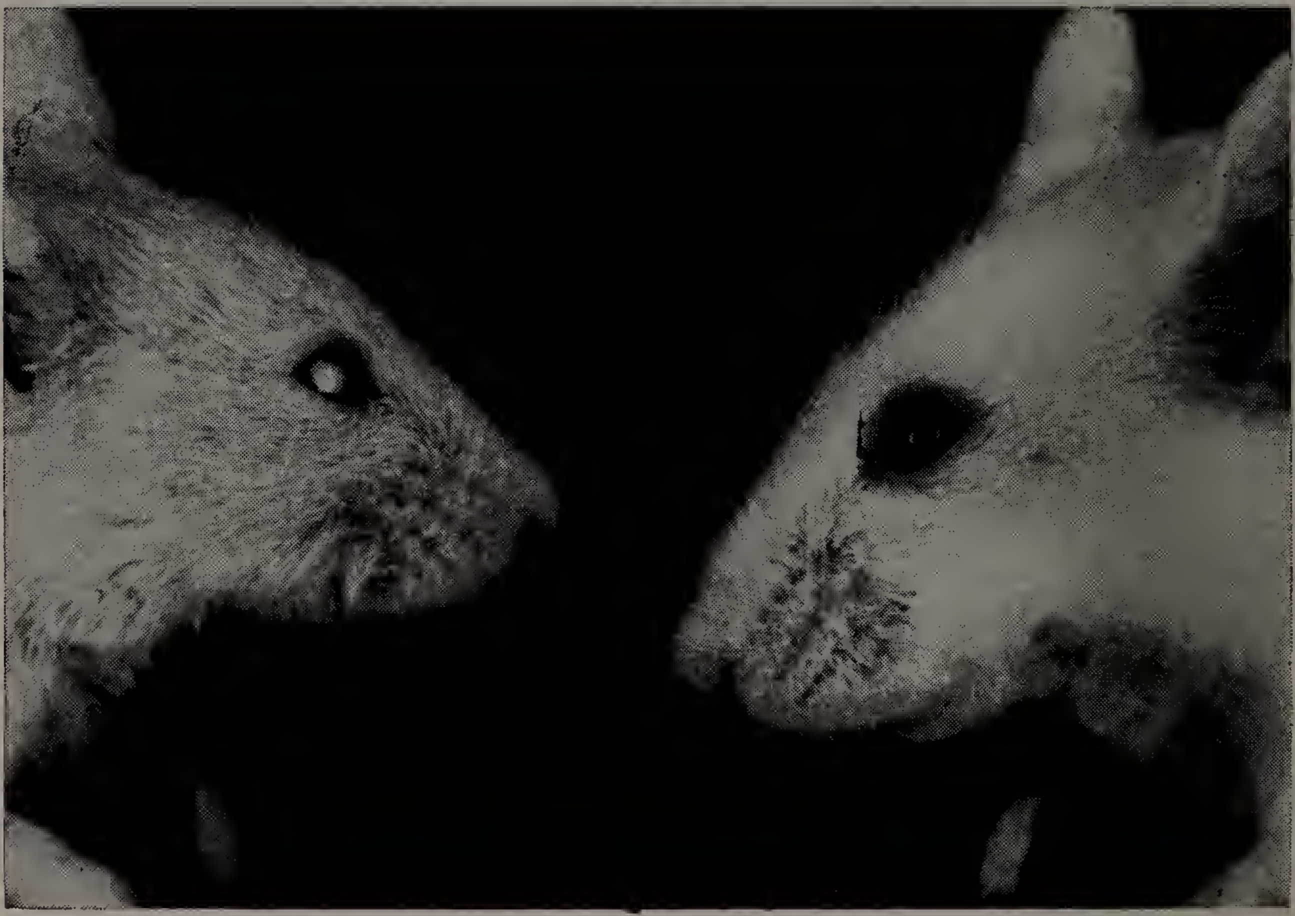
mouth or by drops instilled into the eye. The chief problem in systemic administration has been the strong binding of the inhibitors to serum protein making it difficult to obtain sufficient concentrations within the eye. Present efforts in conjunction with Ayerst Laboratories are being directed toward making structural changes in the molecular configuration of the inhibitors.

At the same time efforts are being made to obtain as much information as possible on the properties of aldose reductase itself. Dr. Jedziniak has been able to isolate this enzyme from calf lenses in highly pure form and analyze some of its properties. The enzyme exists in several different forms. The active form appears to be a dimer of two smaller units, each with a molecular weight of about 20,000. The enzyme is maintained in the active form by the presence of sulfhydryl-containing compounds. In the absence of these sulfhydryl compounds the enzyme becomes inactive and splits to the smaller units. The action of inhibitors like tetramethylene glutaric acid (TMG) is to convert the active form into the inactive form by dissociating the enzyme into the component subunits. This inactivation-dissociation process occurs even in the presence of sulfhydryl compounds.

Another interesting finding is that triphosphopyridine nucleotide (TPN), a product of the reactions, is an effective inhibitor. TPN also inhibits by dissociating the enzyme similar to the action of TMG. It appears that the level of TPN regulates the activity of aldose reductase. If TPN is in the reduced form, TPNH, the activity of the enzyme is maximal. However, as the reaction proceeds and the TPN level is increased, the activity of the enzyme decreases as more of the enzyme is converted to the inactive form. Thus the ratio of TPNH/TPN seems to serve as a regulator of this reaction.

Congenital Cataracts

What are called congenital cataracts in human beings are, in fact, chiefly cataracts that come on in the first few weeks after birth, develop for a variable period of time and then spontaneously cease



What does a cataract in the mouse have to do with cataracts in human beings? The mouse on the left is one of a genetic strain which develop cataracts two weeks after birth while the mouse on the right is a normal control. Dr. Iwata and Mr. Christiansen are documenting the biochemical events that distinguish the cataractous mouse lens from the normal lens in the critical few days after birth. "Congenital" cataracts of human beings similarly develop about two weeks after birth and are presumably due to similar biochemical abnormalities.

to progress further. To learn what went wrong during this early period of development might have important bearing on the understanding of cataracts in general as well as being of significance to the victims of congenital cataracts.

To this end Dr. Iwata, who is spending a year with us, and Mr. Christiansen, who is spending an elective period of his medical school course, have been studying the biochemical parameters of developing lenses in a strain of Japanese mice with hereditary cataracts. A "pin-head" opacity first appears in the lenses of these animals about three weeks after birth. Otherwise the mice grow as well as allied mice which do not develop cataracts. Just prior to the occurrence of the opacity the lenses show a marked increase in sodium and water uptake, but, surprisingly, no detectable decrease in potassium. Yet it has been possible to show that an even earlier change occurs in the capacity of the lenses to concentrate rubidium.

Rubidium exchange is a convenient index of potassium transport and can be used to study the sodium-potassium pump activity. The lenses of mice which are destined to develop congenital cataracts have been found to be unable to concentrate rubidium as early as the eleventh day, that is before any changes have occurred in sodium concentration or hydration. The significance of these observations is that they direct attention to a disturbance in the electrolyte balance as preceding and probably underlying the subsequent development of the cataract.

Cataracts and Glutathione

The physiological role of glutathione (GSH) has never been clearly delineated though it is present in exceptionally high concentration in the lens. Since a loss in GSH is a characteristic of nearly all forms of cataract, it has been suspected that GSH plays a crucial role in maintaining the clarity of the lens. Drs. Kinoshita and Epstein have undertaken to elucidate the importance of GSH in the lens. The approach has been to study the effects of various compounds which are capable of oxidizing glutathione. A special study of diamide, a new compound which is reputed to be a specific oxidant of glutathione, was studied for its effects on the lens. The oxidation of GSH of the lens by diamide was found to result both in a decrease in Na-K pump activity and an increase in permeability to cations. One interesting aspect is that the effects of diamide are observed in lens culture medium without the addition of glucose, but in the presence of glucose no significant loss of glutathione occurred nor were there observed changes in transport of or permeability to cations. Similar effects were also observed with other GSH oxidants such as hydrogen peroxide, iodosobenzoate and azoester on rabbit and rat lenses. The effect of these oxidants was to depress the level of GSH, increase the sodium content and produce swelling of the lens. These effects occurred in the absence of glucose but were also observed in the presence of glucose.

The most reasonable explanation for the observed effects on glutathione and on membrane function is that the level of GSH is normally maintained by the TPNH generated by the direct oxidation of glucose through the pentose shunt mechanism. If the rate of oxidation of GSH is accelerated by oxidants like diamide, an increase in glucose oxidation must occur to generate more TPNH to maintain the GSH level. Apparently there are present on the lens membrane sulfhydryl groups which are unusually susceptible to oxidation when the GSH level is precipitously reduced. These membrane -SH groups are involved in cation pumping as well as in determining the degree of membrane permeability. GSH appears to be necessary to maintain these membrane -SH groups in the reduced form for proper membrane function. It seems likely that the liquefaction of lens fibers caused by excessive swelling, as observed in many types of cataracts, may be the result of changes in membrane function brought about by sulfhydryl oxidation.

The Lens and Red Blood Cells

The metabolic resemblance between the lens of the eye and the red cells of the blood was the subject of a conference organized by Dr. Kinoshita, representing the lens, and Dr. Ernest Beutler representing the red cells. This was held in October at the City of Hope National Medical Center, Duarte, California, with forty conferees in attendance. What brought these two lines of investigation together was a common interest in the glycolytic and control mechanisms which are unique to these two tissues as well as their mutual dependence on glutathione. Lowering of the glutathione level (as in glucose 6-phosphate dehydrogenase deficiency) results in cataracts (in infants) in the case of the eye and in hemolytic anemia in the case of the blood. The conference brought out the interesting observation that liquefaction of lens fibers in cataracts may be comparable to hemolysis in the anemias and that the insolubilization of proteins in cataracts may involve similar mechanisms to those of the familiar Heinz bodies in red cells. Another common bond and subject for further investigation was the observation that sulfhydryl groups play a crucial role in regulating the permeability of both the red cell and of the lens. In both tissues the sulfhydryl groups on the membrane appear to determine the rate of transport of cations, anions, and possibly of sugars.

Glutamine Synthetase, Control Mechanism and the Retina

The enzyme glutamine synthetase must have especial significance for the function and development of the retina. Its concentration is greater in the retina than in any other tissue and it rises abruptly near the end of maturation of the retina. What it is doing there and what the factors are which control its formation have been prime interests of Drs. Liane Reif, Gerald Chader and their team of investigators.

Methods for the assay of glutamine synthetase have been greatly improved so that it is now possible to do short-term experiments previously impossible and to obtain better data. Substantiation has been obtained from a few normal human retinas that high concentrations of the enzyme such as previously found in animal eyes, are also present in human eyes. Similarly, observations on human fetuses have revealed glutamine synthetase as early as 14 weeks postovulation. Even at 35 weeks, the concentration is still very low.

The retina of the newborn rat is comparable to that of the 3-month-old human fetus. It can thus be used as a model for studying what the effects of hormones and other agents may be on the human eye during pregnancy. It has been found that thyroid hormone, administered to the fetal or newborn rat, markedly increases the synthesis of certain retinal enzymes such as the enzyme glutamine synthetase. The hormone thus may play an important role in the biochemical development of the rat retina and possibly the human retina as well. In tissue culture experiments with chick embryo retinas, however, higher concentrations of thyroxine were found to inhibit enzymic synthesis, demonstrating at a molecular level the toxic effects that high levels of thyroid hormones can have on the retina.

Hormones from the adrenal, the corticoids, can also "induce" higher concentrations of the synthetase enzyme in the retina when administered in near physiological amounts to the young rat. When female rats were given larger amounts of the hormone during late pregnancy, however, newborn rats were found to have markedly depressed synthetase levels in the retina at a time when it would normally be in high concentration. This illustrates again the toxic effects that hormones can have on the developing retina.

The chick embryo retina may also be used in tissue culture experiments as a model for studying retinal development. A study has just been completed which pinpoints the structural features of the corticoid hormone molecule that are involved in the induction of the synthetase enzyme in the retina. The uptake rates of hormone into the retina have been determined along with other biochemical parameters which clearly demonstrate that the retina is a true target tissue for corticoid hormone (just as is the uterus for female sex hormones or the kidney for mineralo-corticoids). In this regard, it has been possible to demonstrate the actual presence of corticoid hormone-receptors within the retina. The receptors are macromolecules which bind the hormone with high affinity and which may act as an intracellular transducer through which the hormone influences retinal function.

Since the function of the retina is basically to accept and process light energy, a project has been initiated to ascertain what effects, if any, light may have on biochemical processes in the retina. Within 72 hours of exposure to strong light, retinal synthetase levels have been found to drop to one-half the levels seen in control animals. This may indicate severe biochemical damage to the retina by light and may be analogous to experiments by Dr. Kuwabara which demonstrated profound changes in retinal morphology in the rat after exposure to bright light. Further experiments on this light effect (and conversely, the effects of darkness) are planned.

A pertinent question is where is the glutamine synthetase located in the retina? Contrary to expectation, the enzyme does not appear to be associated specifically with the visual receptor cells as judged from experiments involving mice with hereditary loss of the receptors. These experiments done in conjunction with Dr. Matt LaVail are currently being extended to the occipital cortex.

Effects of Light on the Retina

The electron microscope has served well the study of anatomic changes in the rods and cones induced by exposure to light. Using the xenon arc and laser beam as sources of illumination, Dr. Kuwabara has found that characteristic changes occur in the outer segments of the photoreceptors with only 20% of the energy necessary to produce permanent damage. The rods and cones have a remarkable capacity for repair but require the presence of the overlying pigment epithelium. When this epithelial layer is destroyed, the rods and cones do not recover.

The changes in the outer segments produced by light is similar to that frequently encountered in senile human eyes. One can only wonder, therefore, if certain senile retinopathies have a bearing on the cumulative effect of light exposure. We know of no way to prove it at present.

Yet the destructive effect of light may have beneficial applications in certain cases. Photocoagulation is, for instance, commonly employed in the treatment of diabetic retinopathy. To this end Drs. Shigekuni Okisaka and Lloyd Aiello have been making qualitative and quantitative studies on the reaction of the monkey retina to experimental burns. One of the surprising observations is that the desired vessel occlusion occurs as a secondary process in the repair rather than as a primary result of the exposure.

Diabetes

The major handicap in the study of diabetic retinopathy has been the lack of an animal model in which retinal damage occurs similar to that in human beings. Diabetes occurs spontaneously in various species and may be induced experimentally in most animals but rarely do any develop pathologic changes similar to those which damage the human eye. Dr. Kuwabara has found, however, that the mural cells which are the primary targets in the retinal capillaries of human diabetics are also significantly altered in animal diabetics. Specifically these cells show enlargement and increase in their content of microorganelles. This hyperactivity may be the prelude to disintegration of the mural cells which is the characteristic finding in the late and destructive stage of human diabetes.

Scanning Electron Microscopy

When, a few years ago, scanning electron microscopes became available to record surface contours, Dr. Kuwabara became a pioneer in the application of the new technique to the eye. Our previous Annual Report illustrating the outer segments of the rods and cones showed the dramatic possibilities of studying anatomy by this means. This past year Dr. Kuwabara showed fine irregularities of the corneal surface. These irregularities appear to serve for the maintenance of appropriate moisture of the cornea. Being of a size less than the wave length of light, they cause no scattering of the light rays. Several other tissue surfaces including lens cell interfaces and foot processes of kidney epithelium have also demonstrated the wide usefulness of this technique in histology.

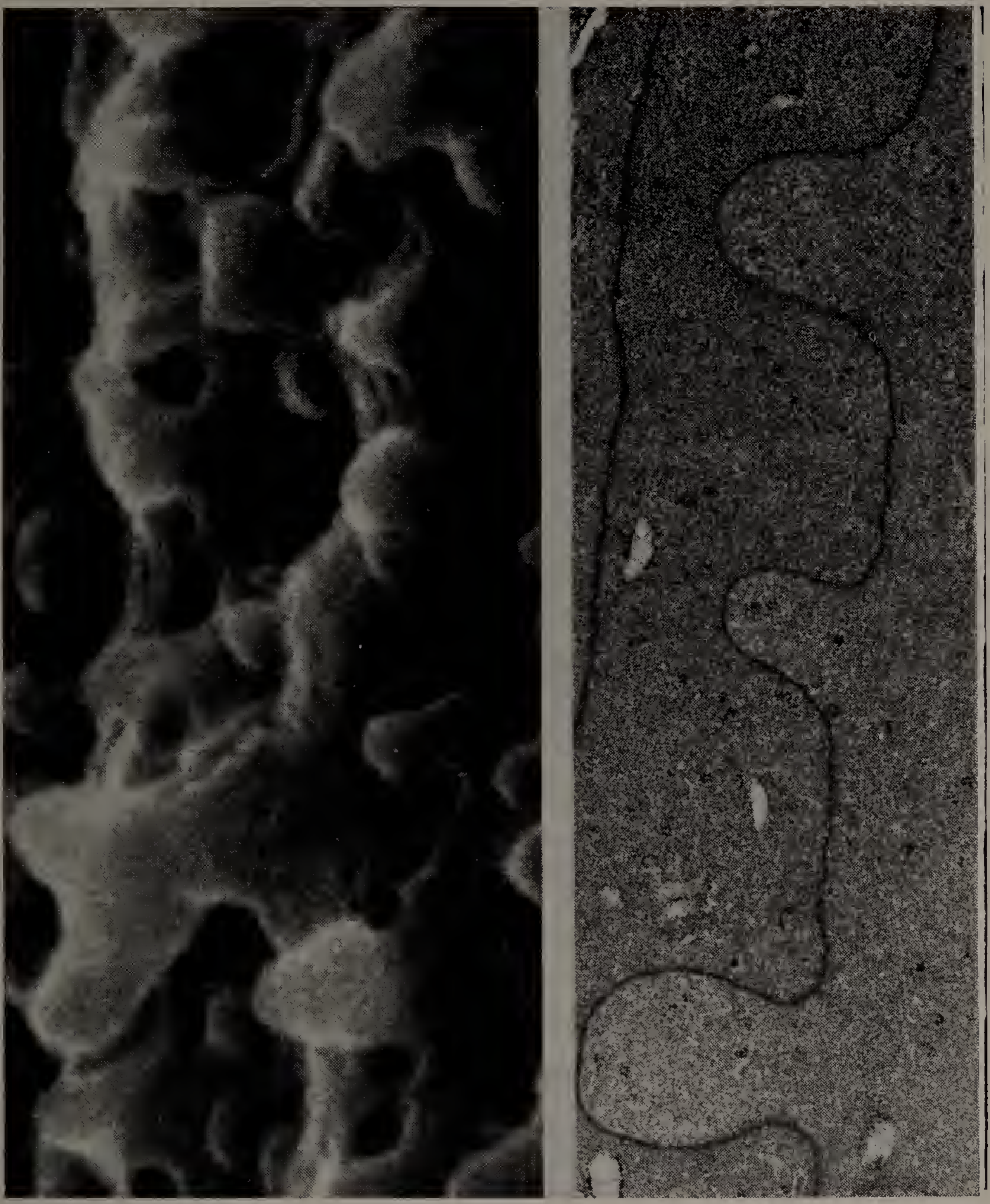
Dr. William Lee began his studies of the trabecular meshwork by scanning electron microscopy and will continue them on his return to Scotland. Specifically, he found by injecting particles of various sizes into the anterior chamber that the endothelium of the meshwork has not only a covering function but an active mechanical function as well. The endothelial cells reacted differently depending on the size and shape of the particle.

Miscellaneous

The characteristics and classifications of *tumors of the ciliary body* were defined and presented for publication by Dr. Cogan on the basis of a review of cases in our files. These tumors represent a wide spectrum of benign and malignant neoplasms of both a mesodermal and epithelial origin. Recognition of their characteristics is an important prelude in deciding which require removal of the eye and which are safe either to remove locally or to leave alone.

The *iris muscles* which control the pupil have certain unusual features, most intriguing of which is the established epithelial origin of the dilator muscle. By studying the developing rat iris by electron microscopy, Dr. Masatoshi Imaizumi has now found that the sphincter muscle has a similar origin. At a stage corresponding to the fifth month of the human fetus, the epithelial cells at the inner margin of the optic cup proliferate to form recognizable smooth muscle.

With a long-standing interest in *cystinosis*, Dr. Kuwabara col-



Electron micrographs illustrating the different views of scanning and transmission electron microscopy at magnifications of approximately 20,000 times. The pictures demonstrate the interdigitations of the normal lens fibers of the eye. That on the left taken with the scanning scope shows the surface contours or zipper-like processes of the fibers while that on the right taken with the transmission scope shows in cross section the interdigitation of these processes in adjacent fibers.

laborated this past year with investigators at the National Institutes of Health to study the distribution of the cystine crystals in eye tissues of patients with this disease. Surprisingly, crystals were found by electron microscopy to be within the cells and specifically within the lysosomes of the cells. This was true for both the fatal type of cystinosis in children and the benign variety of adults.

The pathological changes induced by several possible *poisons* were studied by Dr. Kuwabara, some at the request of the Food and Drug Administration. One of the compounds was the agricultural fungicide 2, 6-Dichloro-4-Nitroaniline which was found to cause corneal opacities in dogs that were exposed to sunlight. Electron micrographs from such corneas revealed crystalline deposits in the extracellular tissue. Some other substances, including hydrocortisone and chloroquine were found to be damaging to the retinas of experimental animals when used in sufficient dosage and especially in animals exposed to bright light.

The pathology of that sometimes blinding disease, temporal arteritis, was further studied by Dr. Kuwabara on consecutive biopsies. Confirming previous observations, the chief abnormalities were found in the muscle cells of the arterial walls.

NEURO-OPHTHALMOLOGY

Course of Instruction

For several years plans to conduct a post graduate course in neuro-ophthalmology in the Boston area have been under discussion. With the prodding of Dr. Thomas Hutchinson representing post graduate education in ophthalmology and the collaboration of many in the local community, such a course was organized this past year by the Laboratory staff (Drs. Cogan, Wray, Kuwabara, Donaldson, Willis and Simpson). To our surprise more than 80 physicians — about equally represented among ophthalmologists, neurologists, and neurosurgeons — enrolled for a week-long discussion of medical matters pertaining to the eye, the brain and the nerves that affect ocular function. The response reflected a strong interest in this subspecialty which crosses the traditional disciplines of medical specialism and encouraged us sufficiently to plan for a repetition of the course this year and possibly in years to come.

Internuclear Ophthalmoplegia

Of a more specific nature has been the clinical study of internuclear ophthalmoplegia. The syndrome which goes by this name has one form which is highly characteristic of multiple sclerosis and another from which is equally characteristic of vascular lesions in the brain stem. Distinction of these two types and recognition of their subtle manifestations is important for proper diagnosis but have not always been made. A retrospective analysis of 200 cases seen by Dr. Cogan over the past quarter century demonstrated the importance of lag in specific eye movements as an asymptomatic sign of internuclear ophthalmoplegia and disclosed categories of internuclear ophthalmoplegia that were caused by neither multiple sclerosis nor vascular disease.

Fluoroangiography

Fluoroangiography has been both a clinical and research tool for the study of retinal circulation. The Howe Laboratory made a small contribution to its usefulness and established its operation at the Infirmary. This past year Dr. Cogan prepared a critique of its place in ophthalmology. But now that fluoroangiography is becoming a routine diagnostic test, its operations are being transferred from the Laboratory to the Infirmary.

Multiple sclerosis

Although multiple sclerosis is a disease of the brain and spinal cord, many cases affect the optic nerves and tracts that control eye movements. It is, therefore, a disease frequently encountered by neuro-ophthalmologists. Its cause is obscure and its diagnosis often uncertain but some evidence suggests a destructive immunosensitivity to one's own brain and spinal cord tissue. To explore this possibility, Dr. Wray is studying the reactions of certain white blood cells, the lymphocytes, in guinea pigs with experimental allergic encephalitis (a disease analogous to multiple sclerosis) and in patients with acute optic neuritis due to multiple sclerosis. Nerve cells are also being grown in culture media to which lymphocytes, spinal fluid, and sera from patients with the disease are added in order to detect specific reactions of their white blood cells. The development of a successful technique for demonstrating transformation of lymphocytes would add substantially to a basic understanding of the disease and possibly provide a convenient blood test for its diagnosis.

Measurement of Retinal and Occipital Signals

The electrical signal generated in the eye by a flash of light is conventionally recorded in the electroretinogram (ERG) and the signal which reaches the brain is recorded over the occiput by the visual evoked response (VER). Dr. Fricker has pioneered an unconventional method of processing the signals by the method of the Synchronous Detector System and by using delay time as the measured parameter rather than simply wave-form.

Dr. Fricker analyzes the electrical signals which reach the brain when the eye is exposed to flashes of light. Data derived from such a test provides clinically important data on the intactness of the visual pathways.

Together with Mr. James Sanders, an electrical engineer, Dr. Fricker has found it possible to test and evaluate retinal rod and cone functions separately. Use of the system at approximately 5 cycles per second, that is considerably lower than originally anticipated, with blue light and low background illumination permits testing of predominant rod function. On the other hand using frequencies of 20 cycles or higher with white or red flash stimuli at normal levels of illumination permits testing of cone function.

A large series of patients have been tested by the foregoing methods. It is apparent that abnormal retinal delay times (for cone function) are associated with gross loss of field due to abnormalities in the retina. This is most striking in the case of retinitis pigmentosa. The method thus provides an objective determination of retinal damage which is independent of opacities in the media. The occipital signals can similarly provide useful information on macular function even in the presence of cataracts. A preliminary series of patients with dense cataracts tested before and after surgery have shown a 70–80% accuracy in predicting "good" post-operative vision.

The advantages of recording by the Synchronous Detector System as compared with traditional methods is being evaluated currently with the help of new equipment which allows waveforms to be recovered from signals with a low signal-to-noise ratio.

Measurement of Eye Movement

To obtain precise data on disturbances of eye movement, Dr. Fricker is currently measuring the ocular excursions by either infrared optical pick-up or by the electrical variations resulting from changes in the position of the eye. Both methods give data on acceleration and velocity that are not obtainable by visual inspection. Dr. Fricker hopes to define the types of movement in various ocular motor abnormalities.

INSTRUMENTATION

Some years ago Dr. Donaldson developed his perimeter which allowed both a central and a peripheral field examination with the same instrument and incorporated features such as monitoring of eye movement and automatic recording of the visual field on a chart. He has now developed an additional mechanism whereby the entire surface of the perimeter is scanned by intermittent flashes of the test object over a period of several minutes. The patient operates a hand switch whenever he sees the test light and this in turn automatically records the extent of the field on the test chart. At any time, the automatic recording device can be disconnected so that the examiner can manually check small details in the central field such as the blind spot. The new adaptation to the perimeter has the advantage of being excellent for a scanning device while maintaining the versatility of the perimeter operated by the examiner.

With the use of finer sutures and microsurgical techniques, the operating room microscope has become increasingly useful. Dr. Donaldson has devised a microscope for use in the operating room which overcomes some of the disadvantages of the pervious operating room microscopes. The instrument is attached to the head of the operator but is counterbalanced in such a way that it can be moved in any direction that is desired by the surgeon. This allows the viewing of the eye from various positions and at various angles, depending on the requirements at the particular moment. Obviously this is impossible with the present instruments which must be left in one position and all operating done in one direction of view. A light source attached to the instrument also moves with the operator's head, assuring excellent lighting at all times.

Dr. Donaldson manipulates the controls of his automatic field testing device.

Measurement of the depth of the anterior chamber can be an important clinical determination. For several years Dr. Donaldson has been interested in developing an instrument which will make this measumerent with a high degree of accuracy. The only satisfactory method previously devised involved photographing a beam of light traversing the anterior chamber and making measurements from the photograph. This method obviously had severe limitations and disadvantages. An instrument recently devised by Dr. Donaldson is an attachment to the slit lamp that allows quick and repeatable measurements of the depth of the anterior chamber with an accuracy within 0.2mm. At present the limitation is that the instrument cannot measure anterior chambers which are less than a millimeter in depth.

TOXICOLOGY

A study has been carried out under Dr. Grant's supervision on damage to the eye by contact with concentrated zinc chloride. Patients who have had splashes of zinc chloride in the form of a solder flux paste or a concentrated solution for galvanizing metals have suffered severe corneal damage with edema of the whole thickness of the cornea persisting for many months. A thorough clinical study of such cases has been made by Dr. Roland Houle, and an experimental study in rabbits to evaluate how long zinc persists in the cornea and whether treatment with chelating agents (intended to extract zinc) might help, have been carried out by Drs. Murray Johnstone and William Sullivan. Experimental studies have shown that a large excess of zinc persists in the cornea for many hours after contamination with concentrated zinc chloride solution, but that treatment by irrigation with the metal chelating agent EDTA must be performed within the first few minutes after the eye is contaminated to have clearly beneficial effect. Studies on excised pieces of cattle cornea by Drs. Johnstone and Sullivan have given evidence of a severe denaturing effect of zinc chloride on the cornea that is not appreciably reversible after exposure to high concentrations of zinc chloride, though it is partially reversible after exposure to low concentrations. It appears from these studies that emergency or first aid irrigation with EDTA solution should be helpful in case of accidents with splashes of zinc chloride but that for later treatment something more effective than EDTA is needed.

VISION INFORMATION CENTER

Discontinuance of the Vision Information Center was one of the major disappointments of the year. The Center was, we thought, a promising venture. It was launched at the request of the then National Institute of Neurologic Diseases and Blindness under the joint auspices of the Howe Laboratory and Countway Library of the Harvard Medical School. Dr. Reinecke became the chief coordinator and developed a staff that prepared the thesaurus and arranged for the necessary computer contacts. With Dr. Reinecke's departure, it seemed logical to transfer the operation to Albany with him. We are now told, however, that restriction of funds from the National Institutes of Health have necessitated a suspension of the project unless alternative funds become available. At the present time, however, it seems to be a casualty of the current fiscal stringency.

A resumé of the Information Center's organization and accomplishments to date together with suggestions for the future development of such a service, was presented in a recent issue of Science (Vol. 169: 29, 1970).

TEACHING AND LEARNING

The Howe Laboratory has been heavily involved in all levels of teaching ever since it established, some years ago, the first intensive course in the ophthalmic basic sciences. This has been, as it should be, of as much benefit to the teachers as to the students and has served to integrate the separate interests of the faculty into concern for the total function of the eye. Several of the texts which have come from the Laboratory owe their genesis in no small measure to these courses.

This past year's teaching activities included a new graduate course in neuro-ophthalmology which is described elsewhere in this report. The two months' elective course for undergraduates, now in its second year under the supervision of Dr. Alfred Scott and Dr. Cogan, is thought to be a unique venture in offering specialized training for prospective ophthalmologists during the medical school years. The "Sunday School Session" just preceding the Infirmary's Alumni Meeting provided again an opportunity to establish a day long dialogue between clinical and laboratory personnel to their mutual profit. Volume III (*Diseases of Cornea and Sclera*) of Dr. Donaldson's stereoscopic *Atlas on External Diseases of the Eye* has been finished and is due for publication in 1971 while Dr. Grant's second and much expanded edition of *Toxicology of the Eye* is approaching the final draft stages. A series of 100 photographs and synopses, entitled *Fundus Abnormalities in Systematic Disease*, has been prepared by Drs. Cogan and Donaldson for distribution by MEDCOM in the near future.

Trainee-investigators in the Laboratory of the past year and their fields of special interests have included: Dr. William Lee, electron microscopy of the out-flow channels; Dr. Ian Macmichael, general ophthalmic pathology; Dr. N. Rodman Willis, neuro-ophthalmology; Dr. E. Rand Simpson, neuro-ophthalmology; Dr. Leo Chylack, lens biochemistry; Dr. David Epstein, lens biochemistry; Dr. Bruce Ellingsen, glaucoma; Dr. Shuzo Iwata, cataract research; Dr. Masatoshi Imaizumi, electron microscopy of iris; Dr. Shigekuni Okisaka, laser effects on retina; Dr. William Holt, corneal immunochemistry; Dr. Brent Lambert, glaucoma; Dr. Joseph Michon, glaucoma; and Dr. David Walton, infantile glaucoma. Some residents who have also found time to work on research problems in the laboratory have included Murray Johnstone (toxicology) and William Sullivan (toxicology).

The expanded elective period of the Harvard Medical School has also given an opportunity for undergraduates to pursue ophthalmic research in some depth. This past year the medical students who elected to spend several months in the Laboratory included John Christiansen, Jesse Sigelman, Jonathan Silver, Richard Meltzer, and Thomas Musliner.

HONORS, AWARDS, AND INVITED LECTURESHIPS

The new professorship made possible by generous donations from the Scaife Family and the Permanent Charity Fund of Boston was officially inaugurated this past year with Dr. Cogan the first incumbent. This is believed to be the first professorship in this country committed to eye research.

The academic custom of inviting faculty members to be resident visitors in other departments has provided opportunities for mutual exchange of interests. This past year Dr. Kuwabara was Visiting Professor to the Department of Ophthalmology at Stanford (January), Dr. Wray to the Department of Neurology at the University of Alberta (February), Dr. Donaldson to the University of Florida, Gainesville (February), Dr. Cogan to the Department of Ophthalmology at Marquette University (May), and Dr. Kinoshita to the Department of Ophthalmology at Washington University (October). Dr. Cogan was the guest speaker of the Michigan Ophthalmological Society, the Bedell Lecturer of the Wills Eye Alumni Association, the Sommers Lecturer of the Oregon Medical Society, the John Brown Lecturer at the Centennial Celebration of the University of Ohio, and the guest lecturer of the Fundación Oftalmologica de Argentina in Buenos Aires.

Dr. Kinoshita had the dsitinction of being the 1970 Chairman of the Board of Trustees of the Association for Research in Ophthalmology and was elected this past year to the Board of Scientific Counselors of the National Eye Institute, National Institutes of Health, for the term 1970–1974.

Dr. Iwata was the 1970 recipient of the Ulmer Award made possible by periodic gifts to the Laboratory by Mr. J. M. Ulmer. Dr. Iwata's highly original researches on congenital cataracts are described elsewhere in this Report.

SUPPORT

In 1940 the total annual budget of the Howe Laboratory and the Howe Library was less than $50,000 with an income derived entirely from endowment. In 1970 the budget is more than ten times this amount with endowment income providing only about one-fifth of the income. For the rest we are dependent on major grants from the National Institutes of Health, the Massachusetts Lions Club, and Research to Prevent Blindness. We are also dependent on the aggregate contribution of other agencies and individuals who include us in their annual charities or choose to commemorate friends or events by contributing to eye research in the Howe Laboratory. We are indeed fortunate to have the backing, moral and monetary, of so many friends who aspire, as we do, to lessen the toll of eye disease and blindness through investing in this humanitarian endeavor.

And finally, I have the great pleasure of announcing that the Howe Laboratory was a major beneficiary in the estate of Dr. William F. O'Reilly in memory of his daughter, F. Lidwine O'Reilly. This gift has special significance from several points of view. In the first place the amount of the gift, just short of $90,000, is the second largest in the Laboratory's history since Dr. Howe's initial funding. Secondly, it comes at a time when cutbacks in government support threaten the continuation of important researches. And thirdly, it will be applied to the capital funds which, although most important for the maintenance of broad research support, are the most difficult to obtain. To Dr. O'Reilly's memory we are, therefore, most grateful and are touched by his assignment of the funds to the name of his daughter who died in infancy. We are also indebted to Drs. Merrill J. King and Robert Trotter who, as former members of the Howe Laboratory staff, represented to Dr. O'Reilly the needs of the Howe Laboratory and the advantages of contributing to eye research in this way.

David G. Cogan, M.D.
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  Neurologic motility disorders.
  Basic aspects of optic nerve disease.

Internuclear ophthalmoplegia, typical and atypical. The Arthur J. Bedell Lecture. Wills Eye Hospital, in Philadelphia, Pennsylvania, February 7, 1970.

Patterns of macula edema. New England Ophthalmological Society, February 11, 1970.

Motor neuro-ophthalmology. Introduction to the Clinic, Third Year Class, Harvard Medical School, February 17, 1970.

Postgraduate Course in Neuro-ophthalmology. Lecture Series. Harvard Medical School, April 13–17, 1970.

What fluoroangiography does and does not show. Wisconsin Medical Society, Ophthalmology Section, in Milwaukee, Wisconsin, May 14, 1970.

Internuclear ophthalmoplegia. Milwaukee Ophthalmological Society, in Milwaukee, Wisconsin, May 14, 1970.

Inborn metabolic errors. Seminars in Medicine, Beth Israel Hospital, May 28, 1970.

Visual agnosia. House Officer Lecture, Massachusetts Eye and Ear Infirmary, June 10, 1970.

Michigan Ophthalmological Society, Summer Conference, in Boyne Highlands, Michigan, July 10–11, 1970:
  What fluoroangiography does and does not show.
  Internuclear ophthalmoplegia.

Neuro-ophthalmology. Postgraduate Course in Ophthalmology, Harvard Medical School, September 22–23, 1970.

The Sommer Memorial Lectures. Oregon Medical Association, in Portland, Oregon, October 8–10, 1970:
  Some common neuro-ophthalmic disorders.
  Ocular manifestations of inborn errors of metabolism.
  Studies on retinal vascular disease.

Vascular retinopathy of retina and choroid. Fundacion Oftalmologica Argentina, in Buenos Aires, Argentina, October 21–24, 1970.

Ocular manifestations of inborn errors of metabolism. The John E. Brown Memorial Lecture. Columbus E.E.N.T. Society, in Columbus, Ohio, November 9, 1970.

Clinical pathology of retinal vasculopathies. Centennial Ophthalmological Symposium, Ohio State University Center for Continuing Medical Education, in Columbus, Ohio, November 10, 1970.

DONALDSON, D. D.

Anatomy of the orbit. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 13–14, 1970.

Morphology of cataracts. New England Ophthalmological Society, April 15, 1970.

Systemic diseases. Department of Continuing Education, Ophthalmology for Internists, Pediatricians and General Practitioners, Harvard Medical School, May 7, 1970.

Ocular diseases in industry. Course in Industrial Ophthalmology, Harvard School of Public Health, May 15 and 22, 1970.

Corneal dystrophies and systemic diseases as they affect the cornea. Postgraduate Course in Corneal Disease, Harvard Medical School, June 11, 1970.

Lancaster Courses in Ophthalmology in Waterville, Maine:
Neuro-ophthalmology, July 20–25, 1970.
External diseases, August 11–15, 1970.

Postgraduate Course in Ophthalmology, Harvard Medical School:
Neuroanatomy, September 1–12, 1970.
Neuro-ophthalmology, October 21–November 16, 1970.
Diseases of the anterior segment, November 23–December 7, 1970.

Essential iris atrophy and Chandler's syndrome. University of Dundee, in Dundee, Scotland, September 26, 1970.

External diseases and ocular photography. University of Pennsylvania Postgraduate Course, in Philadelphia, Pennsylvania, October 13–16, 1970.

Some atrophic conditions of the iris. Buffalo Ophthalmological Club, in Buffalo, New York, December 10, 1970.

ELLINGSEN, B. A.

Glaucoma: Perfusion and the sinusotomy. House Officer Lecture, Massachusetts Eye and Ear Infirmary, April 29, 1970.

FRICKER, S. J.

Optic nerve lesions and degenerative retinopathies. Postgraduate Course in Ophthalmology, Harvard Medical School, March 7, April 11 and October 31, 1970.

Strabismus. House Officer Lecture, Massachusetts Eye and Ear Infirmary, April 1, 1970.

Electrical determination of macular function in eyes with opaque media. Association for Research in Ophthalmology, in Sarasota, Florida, May 3, 1970.

Measurement of horizontal eye motion, velocity and acceleration. New England Ophthalmological Society, May 11, 1970.

Practical ophthalmology for pediatricians. Course in Pediatrics, Harvard Medical School, May 20, 1970.

Eye motion and related parameters. Course in Physiological Optics, Northeastern University, June 1, 1970.

Use of the synchronous detector for ERG and VER measurements in children. International Society for Clinical Electroretinography, in Pisa, Italy, September 7, 1970.

GRANT, W. M.

Aqueous outflow: Physiology and pathologic physiology. Glaucoma Research Conference, in LaCosta, California, March 4–7, 1970.

Toxicity of ophthalmic drugs. House Officer Lecture, Massachusetts Eye and Ear Infirmary, April 8, 1970.

Postgraduate Course in Ophthalmology, Harvard Medical School:
Tonometry and tonography. September 30, 1970.
Toxicology. November 2, 1970.
Glaucoma in infancy and childhood. November 23, 1970.

IWATA, S.

Association for Research in Ophthalmology, in Sarasota, Florida, May 2, 1970:
Biochemical studies on hereditary cataract in mice.
Fractionation of tear mucoids and its physico-chemical properties.

Glutathione, ATP and ascorbic acid levels in cataractous mouse lens. Ophthalmic Biochemistry Conference, in Woods Hole, June 27, 1970.

Hereditary cataract in mice. Alcon Laboratories, in Fort Worth, Texas, October 14, 1970.

The mechanism of hereditary cataract formation in mice. Thompson Biology Laboratory, Williams College, in Williamstown, Massachusetts, November 13, 1970.

JEDZINIAK, J. A.

Inhibition of lens aldose reductase by TPN. Ophthalmic Biochemistry Conference, in Woods Hole, June 27, 1970.

Properties of lens aldose reductase. Lens and Red Cell Symposium, in Duarte, California, October 5–7, 1970.

KINOSHITA, J. H.

Diabetic cataracts. Diabetes Unit, Massachusetts General Hospital January 16, 1970.

Microwave cataracts. Microwave Seminar, Massachusetts Institute of Technology, January 21, 1970.

Series of lectures on the biochemistry of the eye. Department of Ophthalmology, Marquette Medical School, in Milwaukee, Wisconsin, March 18–20, 1970.

Sugar cataracts. Twelfth Annual Research Meeting, Department of Ophthalmology, University of Toronto, in Toronto, Ontario, May 7, 1970.

Series of lectures on the biochemistry of the eye. Lancaster Courses in Ophthalmology, in Waterville, Maine, July 16–17, 1970.

Aldose reductase and its role in sugar cataracts. Gordon Conference on Medicinal Chemistry, Colby College, in Waterville, Maine, August 12, 1970.

Series of lectures on the biochemistry of the eye. Postgraduate Course in Ophthalmology, Harvard Medical School, September 2–4, 1970.

Series of lectures on the biochemistry of the eye. Department of Ophthalmology, Washington University, in St. Louis, Missouri, October 21–23, 1970.

Kuwabara, T.

Anatomy of the macula. New England Ophthalmological Society, February 11, 1970.

Ophthalmic pathology. Department of Pathology, Massachusetts General Hospital, April 7, 1970.

Series of lectures on the anatomy and pathology of the extraocular muscles, retina and optic nerve. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 13–15, 1970.

Structure and function of the retina. Department of Biophysics, University of Virginia Medical School, in Richmond, Virginia, April 20–21, 1970.

Surface structure of the eye. Third IITR Symposium on Scanning Electron Microscopy in Chicago, Illinois, April 28, 1970.

Endoplasmic reticulum of the pigment epithelium. Association for Research in Ophthalmology, in Sarasota, Florida, May 2, 1970.

Scanning electron microscopy. Anatomy Course, Boston University Medical School, May 7, 1970.

Retinal morphology and physiology. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 10, 1970.

Scanning electron microscopy. Albany Medical Center, in Albany, New York, May 15, 1970.

Fine structure of the eye. Northeastern University, May 18, 1970.

Ophthalmic pathology. Department of Pathology, Massachusetts General Hospital, June 2, 1970.

Corneal epithelium. House Officer Lecture, Massachusetts Eye and Ear Infirmary, June 3, 1970.

Anatomy of the cornea. Postgraduate Course in Corneal Disease, Harvard Medical School, June 11, 1970.

Fine structure of the eye. Series of lectures. Lancaster Courses in Ophthalmology, in Waterville, Maine, July 5–9, 1970.

Pathology of diabetic retinopathy. VII International Congress of Diabetes, in Buenos Aires, Argentina, August 26, 1970.

Effect of subthreshold light exposure to the retina. Gordon Conference, in Meriden, New Hampshire, September 3, 1970.

Postgraduate Course in Ophthalmology, Harvard Medical School:
  - Series of lectures on the fine structure of the eye. September–October 1970.
  - Retinal vasculature. December 10, 1970.

Pathology of ptosis. American Academy of Ophthalmology, in Las Vegas, Nevada, October 4, 1970.

Anatomy and pathology of the corneal epithelium. 28th Meeting of the Electron Microscope Society of America, in Houston, Texas, October 6, 1970.

Diabetic retinopathy. Diabetic Unit, Massachusetts General Hospital, October 23, 1970.

Phototherapy and retinal damage. Association for Research in Ophthalmology, in Philadelphia, Pennsylvania, November 6, 1970.

Retinal damage by light. Department of Ophthalmology, University of Illinois Medical School, in Chicago, Illinois, November 18, 1970.

Biological application of scanning electron microscopy. Department of Anatomy, Harvard Medical School, November 24, 1970.

Scanning electron microscopy of the parenchymatous organ. New England Electron Microscopy Society, in Boston, December 2, 1970.

REIF-LEHRER, L.

Control mechanisms in living cells. Postgraduate Course in Ophthalmology, Harvard Medical School, September 1970.

SIMPSON, E. R.

Series of lectures on neuro-ophthalmology. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 12–16, 1970.

Series of lectures on neuro-ophthalmology. Third Year Class, Harvard Medical School, July–December 1970.

Fluorescein angiography. Retina Service, Massachusetts Eye and Ear Infirmary, October 2 and 9, 1970.

Ocular involvement in hematologic disorders. Department of Hematology, Massachusetts General Hospital, October 8, 1970.

Fluoroangiography in diabetes mellitus. Diabetic Unit, Massachusetts General Hospital, October 16, 1970.

Fluoroangiography of the ocular fundus. Postgraduate Course in Ophthalmology, Harvard Medical School, December 15, 1970.

SNYDER, C.

In days of old. New England Ophthalmological Society, April 15, 1970.

Howling Wolf. Ladies Visiting Committee, Massachusetts Eye and Ear Infirmary, May 13, 1970.

Ophthalmic origins. Postgraduate Course in Ophthalmology, September 9 and 11, 1970.

WILLIS, N. R.

Clinical pathology. Elective Course in Ophthalmology, Harvard Medical School, January–February 1970.

Fluoroangiographic characteristics of ocular tumors. New England Ophthalmological Society, February 11, 1970.

Ophthalmoplegia without field loss in pituitary tumors. Neuro-ophthalmic Pathology Symposium, Johns Hopkins Hospital, in Baltimore, Maryland, February 28, 1970.

Fluoroangiography of diabetic retinopathy. Diabetes Unit, Massachusetts General Hospital, March 6, 1970.

Case presentations and discussions. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 13–17, 1970.

Fluorescein angiography: An introduction. House Officer Lecture, Massachusetts Eye and Ear Infirmary, May 13, 1970.

Wray, S. H.

Department of Neurology, University of Alberta, in Edmonton, Alberta, February 14–March 1, 1970.

The neuro-ophthalmic evaluation of the patient.
The diagnosis of ocular myasthenia gravis.
Microcirculation in retinal vascular disease.

Neuro-ophthalmology. Postgraduate Course in Neurology, Massachusetts General Hospital, March 18, 1970.

Member of the Faculty of the American Medical Association Course in Neurology for Internists, Mayo Clinic, in Rochester, Minnesota, March 23–26, 1970.

Ophthalmologic aspects of cerebrovascular disease.
Temporal arteritis.

Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 13–17, 1970.

Motor neuro-ophthalmology. Course in Ophthalmology for Internists, General Practitioners and Pediatricians, Harvard Medical School, May 15, 1970.

Temporal arteritis. Medical Staff, Mt. Auburn Hospital, in Cambridge, May 18, 1970.

Postgraduate Course in Ophthalmology, Harvard Medical School:
Vascular syndromes, October 14, 1970.
Brain stem syndromes, October 21, 1970.
Nystagmus, October 28, 1970.

Ocular manifestations of systemic disease. Medical Staff, Winchester Hospital, in Winchester, December 4, 1970.

FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

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